## REMARKS

### The Office Action

Claims 12, 13, 15, 19-23, and 29-30 are pending in this application. With this reply, claims 31 and 32 have been added. Claims 12, 13, 15, 19-23, and 29-30 stand rejected under 35 U.S.C. § 102(b). Claims 12, 13, 15, and 19-23, and 29-30 stand further rejected under 35 U.S.C. § 103. Applicant addresses these rejections with the following remarks.

### Rejection under 35 U.S.C. § 102(b)

Claims 12, 13, 15, 19-23, and 29-30 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Zhang et al., *J. Pharm. Sci.* 2001 (hereafter "Zhang"). Applicant has addressed this rejection by amendment of claim 12 and with the following arguments.

Zhang teaches the use of a corticosteroid-dextran prodrug conjugate for the treatment of inflammatory conditions. See, for example, Zhang at page 2079, right column, which recites:

> Dextran-methyprednisolone succinate (DMP), a conjugate of MP and dextran containing two ester bonds, was synthesized using succinic acid as a linker between the polymer and MP (Scheme 1). Hydrolysis studies showed that at physiological pH, DMP is slowly hydrolyzed at both ester bonds (Scheme 1), resulting in the formation of MP and methylprednisolone succinate (MPS), the latter being subsequently converted to MP.

The corticosteroid conjugate of Zhang is designed to be cleaved *in vivo*, releasing methyprednisolone succinate and methyprednisolone. The purpose of the Zhang's conjugate is to target the corticosteroid to the liver and spleen. Once delivered to the targeted site, the conjugate is cleaved, releasing unconjugated corticosteroid at the site. See, for example, Zhang in the abstract, which recites:

> As for tissue distribution, the conjugate delivered the steroid primarily to the spleen and liver as indicated by 19- and 3-fold increases, respectively, in the tissue/plasma area under the curve (AUC) ratios of the steroid. On the other hand, the tissue/plasma AUC ratios of the prodrug in other organs were negligible. Active MP was released from DMP slowly in

the spleen and liver, and AUCs of the regenerated MP in these tissues were 55- and 4.8-fold, respectively, higher than those after the administration of the parent drug.

The Examiner has noted that the conjugates of Zhang slowly hydrolyze *in vivo* and have a much longer half-life than unconjugated methylprednisolone. On this basis the Examiner concludes that the conjugates of Zhang are inherently resistant to *in vivo* cleavage (the Office Action at page 5) as defined in the pending claims. Applicants respectfully disagree.

*The conjugates of the invention are distinguished from Zhang by their resistance to in vivo cleavage.*

As amended, claim 12, and dependent claims 13-15, 19-23, and 29-30, include the limitation that the corticosteroid conjugate is resistant to *in vivo* cleavage such that *in vivo* less than 10% of the administered corticosteroid conjugate is cleaved, separating said corticosteroid from said group, prior to excretion. This amendment has been made to clarify that resistance to *in vivo* cleavage refers **not to the rate** at which cleavage occurs *in vivo*, but rather **the extent** to which cleavage occurs prior to excretion.

While the conjugate of Zhang degrades slowly, it is not resistant to *in vivo* cleavage as defined in Applicant's specification. Following intravenous injection Zhang's conjugate first resides largely in the plasma compartment with a half life (in the plasma compartment) of 6.3 hours (see Table 1, page 2082 of Zhang). The conjugate then distributes largely into the liver and spleen, where further degradation releases methylphenidate (i.e., as "regenerated MP," see Table 2, page 2083 of Zhang) in these tissues. The conjugate has a half-life of 35.9 hours and 52.9 hours in the liver and spleen, respectively ($t_{1/2}$ calculated from $\lambda_z$ in Table 2 of Zhang using the equation $t_{1/2} = 0.693/\lambda_z$). The kinetics of hydrolysis for the conjugate has been reported by Mehvar (Mehvar et al., *J. Control. Release* 68:53 (2000) submitted herewith). Mehvar shows that in blood about 5% of the conjugate is hydrolyzed at 3 hours (see Mehvar at page 54, right

column) and the half-life for hydrolysis of the conjugate (the time at which 50% of the conjugate has been hydrolyzed) in blood is about 25 hours (see Mehvar at page 59, left column). The pharmacokinetic and hydrolysis data reported for Zhang's conjugate has been reviewed by Dr. Teicher, an inventor of the claimed subject matter. In view of these data, Dr. Teicher is of the opinion that at least 50% of the DMP conjugate would be cleaved prior to clearance. See Teicher Declaration at ¶ 3.

In contrast to the dextran conjugate described by Zhang, the claims of the present invention are directed to the use of corticosteroid conjugates that resist cleavage *in vivo* to avoid potentially harmful exposure of the central nervous system to unconjugated steroid. See the specification at page 21, lines 15-22, which recites:

> The corticosteroid conjugates of the present invention are designed to largely remain intact in vivo, resisting cleavage by intracellular and extracellular enzymes (e.g., amidases, esterases, and phosphatases). Any in vivo cleavage of the corticosteroid conjugate produces the parent steroid, resulting in the unnecessary and potentially harmful exposure of the central nervous system to this corticosteroid. Thus, the corticosteroid conjugates of the invention are not prodrugs, but are therapeutically active in their conjugated form, resulting in an improved therapeutic index relative to their parent, unconjugated, corticosteroid.

Because Zhang teaches the use of corticosteroid conjugate prodrugs which slowly undergo extensive hydrolysis prior to excretion, Zhang is not relevant to the novelty of the pending claims.

In view of the amendment to claim 12 and the arguments above, Applicant requests withdrawal of the rejection for lack of novelty.

Rejection under 35 U.S.C. § 103(a)

Claims 12, 13, 15, 19-23, and 29-30 stand rejected under 35 U.S.C. § 103 for obviousness over Zhang. Applicant has addressed this rejection by amendment of claim 12 and with the following arguments.

> *To find the invention obvious, the*
> *prior art must contain both a suggestion of*

*the modification and an expectation of success.*

In moving from the prior art to the claimed invention, one cannot base a determination of obviousness on what the skilled person might try or find obvious to try. Rather, the proper test requires determining what the prior art would have led the skilled person to do. In evaluating obviousness, one must look to see if "the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art.... Both the suggestion and the expectation of success must be founded in the prior art, not in the Applicant's disclosure." *In re Dow Chemical Co. v. American Cyanamid Co,* 837 F.2d 469, 5 USPQ2d 1529.

*Zhang teaches away from the use of conjugates resistant to in vivo cleavage.*

Zhang clearly states that to be effective the conjugate must be designed to release methylphenidate *in vivo*. See Zhang at page 2084, right column, which recites:

> Recent studies[29] in our laboratory demonstrated that DMP by itself lacks a significant immunosuppressive activity and should release MP to be effective.

Accordingly, Zhang teaches away from the claimed invention. More importantly, Zhang fails to suggest the desirability of conjugates resistant to *in vivo* cleavage. A suggestion of the claimed modification is a required element of the Examiner's case of *prima facie* obviousness. This element is missing and the rejection should be withdrawn.

Finally, Applicant notes that the courts have repeatedly recognized that proceeding contrary to the accepted wisdom in the art represents "strong evidence of unobviousness." See *In re Hedges,* 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986); *WL. Gore & Assocs., Inc. v. Garlock, Inc.,* 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983); and *In re Fine,* 837 F.2d at 1074, 5 USPQ2d at 1599 (Fed. Cir. 1988).

In view of the amendment to claim 12 and the arguments above, Applicant requests withdrawal of the rejection for obviousness.

Support for the Amendment to claim 12 and new claims 31 and 32

Claim 12 has been amended to include the limitation that the corticosteroid conjugate is "is resistant to *in vivo* cleavage, such that *in vivo* less than 10% of the administered corticosteroid conjugate is cleaved, separating said corticosteroid from said group, prior to excretion." Support for this limitation is found in the specification at page 10, lines 3-5.

Support for new claim 31 and 32 is also found in the specification at page 10, lines 3-5.

No new matter has been added with these amendments.

## CONCLUSION

Applicants submit that the claims are now in condition for allowance and such action is respectfully requested. To expedite prosecution applicants request a telephonic interview with the Examiner to discuss any remaining rejections. The Examiner is invited to call the undersigned at 617-428-0200.

Enclosed is a Petition to extend the period for replying to the Office action for 3 months, to and including May 30, 2006, and a check in payment of the required extension fee.

Also enclosed is a check for $50.00 for the two new dependent claims. If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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